



Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville MD 20852-1448

OCT 21 1999

CBER-99-002

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John E. O'Brian
Head of Primary Production
Medeva Pharma Ltd
Gaskill Road, Speke
Liverpool, United Kingdom L24 9GR

Dear Mr. O'Brian:

The Food and Drug Administration (FDA) conducted an inspection of your facility located at Gaskill Road, Speke, Liverpool, UK, between July 13 and July 21, 1999. During the inspection, our inspectors documented significant deviations from the applicable standards and requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21 Code of Federal Regulations (21 CFR), Parts 211 and 600-680 as follows:

1. Failure to establish and follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that:
 - a. Fluvirin™ post ultra filtration () monovalent pool samples (e.g., batch numbers 751140, 751201, 751288, 751293, 751485, and 751707) exceeded the bioburden internal specification of < 1 colony forming unit (cfu)/milliliter (ml) with bioburden levels ranging from 1 cfu/ml to 1 cfu/ml. These monovalent pools were refiltered and used to formulate influenza virus vaccine.
 - b. The sterile filtration and blending processing steps of Fluvirin™ monovalent pool and trivalent bulk have not been qualified since 1993 and 1992 respectively.

- c. The processing hold times for pooled zonal concentrate and split antigen concentrate have not been validated.
 - d. Fluvirin™ reprocessing standard operating procedure (SOP BLE024) does not include the number of times a reprocessing step can be repeated and a time limit for re-filtration of monovalent pool with high bioburden results.
 - e. Stability data is not available to demonstrate that refiltered monovalent blend does not affect the stability of the final drug product (Fluvirn™.)
- 2. Failure to ensure that reprocessed batches will conform with all established standards, specifications, and characteristics [21 CFR 211.115(a)] in that any monovalent blend pool with unacceptable endotoxin level may be reprocessed by [REDACTED] and concentration in the [REDACTED] ultrafiltration system; however, there is no data available to demonstrate that this system has been validated to remove unacceptable levels of endotoxin.
 - 3. Failure to establish a written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)] in that there is no data available to demonstrate that through the influenza virus vaccine shelf life the thimerosal concentration is adequate to control bacteria and fungi and the vaccine is sterile since preservative content and sterility testing are not done at expiry.
 - 4. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)] in that cleaning validation studies of all product contact equipment such as the [REDACTED] ultra filtration unit have not been completed.
 - 5. Failure to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that:
 - a. The clean steam system servicing the manufacturing areas after the inactivation stage has not been monitored for conductivity, TOC, and endotoxins since November 1998.
 - b. There is no documentation that during the aseptic media fills done to the syringe and vial filling units all planned interventions that occur during routine production activities were simulated.
 - 6. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mixups [21 CFR 211.42(c)] in that data is not available to demonstrate that adequate pressure differential is maintained

during filling operations since pressure is monitored _____

We acknowledge receipt of your response dated September 1, 1999, to the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

1. Please provide data to support the further processing of intermediates (monovalent blend pool and split antigen concentrate) that exceeded the bioburden and endotoxin internal specifications. In lieu of the final investigation report into the bioburden levels in the process fluid stage of the Influenza Virus Vaccine manufacture, please submit a detailed summary of the conclusions upon completion of the investigation.

Please provide the rationale for increasing your internal specifications when your investigation as to the cause of elevated bioburden and endotoxin levels has not been completed.

2. Please provide a list of all the critical process steps and the specific test methods used to evaluate those critical process steps during the process validation study for the Influenza Virus Vaccine. Also, please be advised that in the absence of data to support holding times for intermediate products, minimal hold times should be in place until the process validation has been completed.
- 3b. Although your investigation regarding the cause of elevated bioburden and endotoxin levels has not been completed, you amended your procedure to define the endotoxin and bioburden levels requiring reprocessing. Please provide data to support the selection of these reprocessing levels. Also, please be advised that it is unacceptable to mix monovalent blend pools that exceeded the endotoxin internal specification with monovalent blend pool that met internal endotoxin specification.

The proposed bioburden limit of _____ cfu prior to sterile filtration, as stated in your written procedure BLE024, is unacceptable. The bioburden limit prior to sterile filtration should be based on historical data rather than the bacterial retention capabilities of the sterilizing filter. Please adjust your bioburden limit accordingly.

- 3d. Please adjust the limit requiring microbial speciation prior to sterile filtration of monovalent blend pool to reflect the new microbial limit selected at this stage of manufacturing.
4. Please provide a summary of the approximately 24 deviation reports that you were not able to locate during the inspection including the type of deviation, at what stage of the process the deviation occurred, and any corrective action(s) implemented.

11. Regarding the two Media Simulation Tests (POP042 and POP074):

- a. Please clarify whether a single media fill is defined as a total of _____ units filled per _____ interventions or _____ units filled per intervention.
- b. The media fill protocols do not include the allowable number of contaminants per designated number of filled units.
- c. The protocols do not include the set-up procedures or reference all the steps necessary for media fills as indicated in the aseptic filling validation procedure.

Regarding the Syringe Filling Line Process Simulation Test (POP042), the protocol steps for gloves replacements do not always correlate with the instructions and documentation of glove replacements on the recording worksheets.

Regarding the _____ Filling Line Process Simulation Test (POP074), the protocol does not reference the fill size or the frequency of all interventions such as the addition of stoppers and caps during the fill.

15. Please be advised that the proposed routine monitoring frequency of the clean steam system should be based on historical data.
16. Please be advised that the proposed routine monitoring frequency of the compressed air system should be based on historical data.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations.

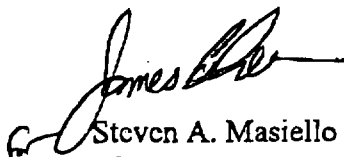
You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include license suspension and/or revocation. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within 15 working days of receipt of this letter, of any additional specific steps you have taken to correct the noted deviations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Page 5 – Mr. John E. O'Brian

Your reply should be sent to the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville pike, Suite 200N, Rockville, MD 20852-1448.

Sincerely,

A handwritten signature in black ink, appearing to read "Steven A. Masiello", with a stylized flourish at the end.

Steven A. Masiello
Director

Office of Compliance and Biologics Quality
Center for Biologics Evaluation and
Research